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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,517	01/14/2002	Imre Kovesdi	212518	3747

23460 7590 07/28/2003

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EXAMINER
DAVIS, RUTH A

ART UNIT	PAPER NUMBER
1651	5

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/046,517	KOVESDI ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *15-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed May 16, 2003 has been received and entered into the case.

Applicant's election affirmation with traverse of Group I, claims 1 – 14 in Papers No. 3 and 4 is acknowledged. The traversal is on the grounds that the inventions overlap and the search for one invention would turn up those of the other inventions. This is not found persuasive because as indicated by separate classification, the inventions are separated and distinct. Further, an overlapping search is not a coextensive search. As such, a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1 – 26 are pending, claims 15 – 26 are withdrawn from consideration and claims 1 – 14 have been considered on the merits. All arguments have been fully considered.

Claim Rejections - 35 USC § 112

Rejections under 35 U.S.C. 112, second paragraph, are withdrawn due to amendment.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kuma (EP).

Applicant claims a composition for maintaining a non-enveloped viral vector, the composition comprising about 1 – 25% trehalose; about 0.02 – 2 mM divalent metal salt, cationic polymer or combination thereof; a multiplicity of non-enveloped viral vector particles; and a liquid carrier, wherein the viral vector is an adenovirus.

Kuma teaches preserving viruses by adding 1 – 10% arginine, 1 – 10% trehalose, polyethylene glycol (cationic polymer) and buffer to an adenovirus (col.5 line 41 – col.6 line 28).

Kuma does not teach the claimed amounts of cationic polymer. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the amounts of known effective ingredients as a matter of routine experimentation. Therefore, at the time of the claimed invention, one of ordinary skill in the art

would have been motivated by routine practice to optimize the volumes of each of the ingredients of Kuma with a reasonable expectation for successfully obtaining a composition for preserving viruses.

Applicant argues that Kuma does not teach the amount of cationic polymer.

However, this argument fails to persuade because as stated above, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to optimize volumes of active ingredients as a matter of routine experimentation. Absence of evidence to the contrary, the claimed amount does not appear to impart unexpected benefits or results to the optimized composition of Kuma, and is therefore rendered obvious.

4. Claims 1 – 3 and 6 – 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Herrmann.

Applicant claims a composition for maintaining a non-enveloped viral vector, the composition comprising about 1 – 25% trehalose; about 0.02 – 2 mM divalent metal salt, cationic polymer or combination thereof; a multiplicity of non-enveloped viral vector particles; and a liquid carrier. Specifically the composition comprises about 0.05 – 2 mM divalent metal salt, or 0.05 – 2 mM MgCl2. The composition further comprises a buffer, such that the pH is about 6 – 9 at 25C and 10 – 65 mM arginine. The concentration of non-enveloped viral vectors are about 1X10^5 – 1X10^13 PFU/ml, the osmolality of the liquid composition is about 150 – 800 mOsM, the ionic strength of the liquid composition is about 10 – 200 mM.

Herrmann teaches stabilizing viral particles by adding thereto a saccharide, buffer and water (abstract). Specifically, compositions of buffer, 1 – 12% trehalose, 0.03% or less NaCl and 0.1 – 10% arginine are combined with a retrovirus to obtain an aqueous solution with a pH of about 7.4 (col.3, example 3). Other salts may also be added such as magnesium chloride (col.7 line 1-5).

Herrmann does not specifically teach the claimed amounts of each ingredient, the claimed osmolality or ionic strength. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the amounts of known effective ingredients as well as osmolalities and ionic strengths as a matter of routine experimentation. Therefore, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the parameters of the composition of Herrmann with a reasonable expectation for successfully obtaining a composition for stabilizing viruses.

Applicant argues that Herrmann does not teach the claimed amount of divalent salt.

However, this argument fails to persuade because as stated above, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to optimize volumes of active ingredients as a matter of routine experimentation. Absence of evidence to the contrary, the claimed amount does not appear to impart unexpected benefits or results to the optimized composition of Herrmann, and is therefore rendered obvious.

5. Claims 1 – 9 and 11 – 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (US) or Evans (WO).

Applicant claims a composition for maintaining a non-enveloped viral vector, the composition comprising about 1 – 25% trehalose; about 0.02 – 2 mM divalent metal salt, cationic polymer or combination thereof; a multiplicity of non-enveloped viral vector particles; and a liquid carrier. Specifically, the composition comprises about 0.05 – 2 mM divalent metal salt, or 0.05 – 2 mM MgCl2. The composition further comprises a nonionic surfactant in about 0.001 – 0.015%, wherein the nonionic surfactant is polysorbate 80; and a buffer, such that the pH is about 6 – 9 at 25C. The concentration of non-enveloped viral vectors are about 1X10^5 – 1X10^13 PFU/ml, the osmolality of the liquid composition is about 150 – 800 mOsM and the ionic strength of the liquid composition is about 10 – 200 mM. The viral vector is an adenoviral vector and is replication deficient.

Evans (US) teaches viral compositions comprising a liquid adenovirus, buffer, sugar, salt, divalent cation and non-ionic detergent (abstract). The compositions are disclosed to maintain viral stability for up to 2 years at temperatures of 2 – 8C and higher (0004, 0012). Specifically, the composition comprises an adenovirus in an amount of 1x10^7 virus particles/milliliter – 1x10^13 particles/milliliter (0050). Non-ionic surfactants include polysorbate 80 (0051) at about 0.001 – 1% (0059), divalent cations include MgCl2 at about 0.1 – 5 mM (0052), and the 2 – 8% sugar/cryoprotectant may be trehalose (0053, 0060, 0061). Evans (US) teaches the salts are added to attain the desired ionic strength and osmolarity (0054) with preferred osmolarties between 200 – 800 mOs/L (0056) and a preferred pH of 7.5 – 8.5 (0059).

Evans (WO) teaches viral compositions comprising a liquid adenovirus, buffer, sugar, salt, divalent cation and non-ionic detergent (abstract). The compositions are disclosed to maintain viral stability for up to 2 years at temperatures of 2 – 8C and higher (p.1,3). Specifically, the composition comprises an adenovirus in an amount of 1x10^7 virus particles/milliliter – 1x10^13 particles/milliliter (p.8). Non-ionic surfactants include polysorbate 80 (p.9) at about 0.001 – 1% (p.11), divalent cations include MgCl2 at about 0.1 – 5 mM (p.9), and the sugar may be trehalose (p.9). Evans (WO) teaches the salts are added to attain the desired ionic strength and osmolarity (0054) with preferred osmolarties between 200 – 800 mOs/L (p.10) and a preferred pH of 7 – 9 (p.8).

The references do not teach the compositions with the claimed ionic strength, or wherein the virus is replication deficient. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the parameters of the compositions of Evans (US) and/or Evans (WO) as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the parameters of the above compositions with a reasonable expectation for successfully obtaining a composition for maintaining a viral vector.

Applicant argues that the references do not teach the claimed amount of trehalose.

However, this argument fails to persuade because as stated above, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to optimize volumes of active ingredients as a matter of routine experimentation. Absence of evidence to the

contrary, the claimed amount does not appear to impart unexpected benefits or results to the optimized compositions of the references, and is therefore rendered obvious.

6. Claims 1 – 2 and 4 – 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kovesdi (WO).

Applicant claims a composition for maintaining a non-enveloped viral vector, the composition comprising about 1 – 25% trehalose; about 0.02 – 2 mM divalent metal salt, cationic polymer or combination thereof; a multiplicity of non-enveloped viral vector particles; and a liquid carrier. Specifically, the composition comprises about 0.05 – 2 mM divalent metal salt. The composition further comprises a nonionic surfactant in about 0.001 – 0.015%, wherein the nonionic surfactant is polysorbate 80; a buffer, such that the pH is about 6 – 9 at 25C; and about 10 – 65 mM arginine. The concentration of non-enveloped viral vectors are about 1X10^5 – 1X10^13 PFU/ml, the osmolality of the liquid composition is about 150 – 800 mOsM and ionic strength of the liquid composition is about 10 – 200 mM. Finally, the viral vector is a replication deficient adenoviral vector.

Kovesdi teaches a composition for preserving a virus, the composition comprising a liquid carrier, viral particles, polysorbate 80, L-arginine and trehalose (abstract). The composition additionally comprises adenovirus (p.2 line 31-34, p.3 line 11-19), tris buffer, and salts (p.3 line 26-30). The trehalose is present at about 2 – 10%, the polysorbate is present at about 0.001 – 0.01% (p.4 line4-12) while the temperature is from 2 – 37C (p.5 line 27-34), and the pH is from 6 – 9 (p.6 line 32-37). Kovesdi teaches the compositions comprising divalent metal salts to include MgCl2 (examples).

Kovesdi does not teach the composition with the claimed amounts of each ingredient, ionic strength, osmolality, or wherein the virus is replication deficient. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the amounts of known effective ingredients as well as the parameters of the compositions of Kovesdi as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the parameters of the disclosed composition with a reasonable expectation for successfully obtaining a composition for preserving a virus.

Applicant argues that Kovesdi does not teach trehalose with MgCl2.

However, this argument fails to persuade because Kovesdi teaches the compositions wherein trehalose may be combine with MgCl2 (examples). At the time of the claimed invention, one of ordinary skill in the art would have been motivated by Kovesdi to combine any of the disclosed sugar/salt combinations and optimize the volumes of active ingredients as a matter of routine experimentation. Absence of evidence to the contrary, the claimed combination does not appear to impart unexpected benefits or results to the composition of Kovesdi, and is therefore rendered obvious.

7. Claims 1 – 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (US) or Evans (WO) in view of Kovesdi (WO).

Applicant claims a composition for maintaining a non-enveloped viral vector, the composition comprising about 1 – 25% trehalose; about 0.02 – 2 mM divalent metal salt,

cationic polymer or combination thereof; a multiplicity of non-enveloped viral vector particles; and a liquid carrier. Specifically the composition comprises about 0.05 – 2 mM divalent metal salt, or 0.05 – 2 mM MgCl2. The composition further comprises a nonionic surfactant in about 0.001 – 0.015%, wherein the nonionic surfactant is polysorbate 80; a buffer, such that the pH is about 6 – 9 at 25C; and about 10 – 65 mM arginine. The concentration of non-enveloped viral vectors are about 1X10^5 – 1X10^13 PFU/ml, the osmolality of the liquid composition is about 150 – 800 mOsM, the ionic strength of the liquid composition is about 10 – 200 mM. Finally, the viral vector is a replication deficient adenoviral vector.

Evans (US) teaches viral compositions comprising a liquid adenovirus, buffer, sugar, salt, divalent cation and non-ionic detergent (abstract). The compositions are disclosed to maintain viral stability for up to 2 years at temperatures of 2 – 8C and higher (0004, 0012). Specifically, the composition comprises an adenovirus in an amount of 1x10^7 virus particles/milliliter – 1x10^13 particles/milliliter (0050). Non-ionic surfactants include polysorbate 80 (0051) at about 0.001 – 1% (0059), divalent cations include MgCl2 at about 0.1 – 5 mM (0052), and the 2 – 8% sugar/cryoprotectant may be trehalose (0053, 0060, 0061). Evans (US) teaches the salts are added to attain the desired ionic strength and osmolarity (0054) with preferred osmolarties between 200 – 800 mOs/L (0056) and a preferred pH of 7.5 – 8.5 (0059).

Evans (WO) teaches viral compositions comprising a liquid adenovirus, buffer, sugar, salt, divalent cation and non-ionic detergent (abstract). The compositions are disclosed to maintain viral stability for up to 2 years at temperatures of 2 – 8C and higher (p.1,3). Specifically, the composition comprises an adenovirus in an amount of 1x10^7 virus particles/milliliter – 1x10^13 particles/milliliter (p.8). Non-ionic surfactants include polysorbate

80 (p.9) at about 0.001 – 1% (p.11), divalent cations include MgCl2 at about 0.1 – 5 mM (p.9), and the sugar may be trehalose (p.9). Evans (WO) teaches the salts are added to attain the desired ionic strength and osmolarity (0054) with preferred osmolarties between 200 – 800 mOs/L (p.10) and a preferred pH of 7 – 9 (p.8).

The references do not teach the compositions further comprising arginine. However, Kovesdi teaches a composition for preserving a virus, the composition comprising a liquid carrier, adenoviral particles, polysorbate 80, L-arginine and trehalose (abstract, p.2 line 31-34, p.3 line 11-19). At the time of the claimed invention, one of ordinary skill in the art would have been motivated to include arginine in the compositions of Evans (US) or Evans (WO) because of the known and disclosed use to preserve viruses. Moreover, at the time of the claimed invention, one or ordinary skill in the art would have been motivated to combine arginine to the composition of Evans (US) and/or Evans (WO) with a reasonable expectation for successfully obtaining a composition for preserving and maintaining viral compositions.

The references do not teach the compositions with the claimed ionic strength, or wherein the virus is replication deficient. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the parameters of the compositions of Evans (US) and/or Evans (WO) as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the parameters of the above compositions with a reasonable expectation for successfully obtaining a composition for maintaining a viral vector.

Applicant does not provide arguments to this particular rejection, and is therefore maintained for the reasons above.

It is noted that applicant addresses a combination of Evans (US) and Evans (WO) and Kovesdi '943 or '289 as in the Obvious Double Patenting Rejection. However, applicant fails to address the combination above.

8. Claims 1 – 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kovesdi (WO) in view of Frei.

Applicant claims a composition for maintaining a non-enveloped viral vector, the composition comprising about 1 – 25% trehalose; about 0.02 – 2 mM divalent metal salt, cationic polymer or combination thereof; a multiplicity of non-enveloped viral vector particles; and a liquid carrier. Specifically the composition comprises about 0.05 – 2 mM divalent metal salt, or 0.05 – 2 mM MgCl2. The composition further comprises a nonionic surfactant in about 0.001 – 0.015%, wherein the nonionic surfactant is polysorbate 80; a buffer, such that the pH is about 6 – 9 at 25C; and about 10 – 65 mM arginine. The concentration of non-enveloped viral vectors are about 1X10^5 – 1X10^13 PFU/ml, the osmolality of the liquid composition is about 150 – 800 mOsM, the ionic strength of the liquid composition is about 10 – 200 mM. Finally, the viral vector is a replication deficient adenoviral vector.

Kovesdi teaches a composition for preserving a virus, the composition comprising a liquid carrier, viral particles, polysorbate 80, L-arginine and trehalose (abstract). The composition additionally comprises adenovirus (p.2 line 31-34, p.3 line 11-19), tris buffer, and salts (p.3 line 26-30). The trehalose is present at about 2 – 10%, the polysorbate is present at

about 0.001 – 0.01% (p.4 line4-12) while the temperature is from 2 – 37C (p.5 line 27-34), and the pH is from 6 – 9 (p.6 line 32-37). Kovesdi teaches the compositions comprising divalent metal salts to include MgCl2 (examples).

Kovesdi does not teach the composition with the claimed amounts of each ingredient, ionic strength, osmolality, or wherein the virus is replication deficient. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the amounts of known effective ingredients as well as the parameters of the compositions of Kovesdi as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the parameters of the disclosed composition with a reasonable expectation for successfully obtaining a composition for preserving a virus.

Kovesdi does not teach a specific composition of trehalose and MgCl2. However, Frei teaches compositions comprising adenoviral particles buffered to maintain a pH of 7 – 8.5 in the temperatures of 2 – 27C (abstract,p.8) wherein the compositions comprise about 5 – 25 mg/mL disaccharides, about 1x10^9 – 1X10^13 viral particles/mL (p.7), about 0.1 – 1 mg/mL divalent metal salts (magnesium salts) (p.5), diluents and about 0.01 – 0.3 mg/mL polysorbate 80 (p.7).

At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use magnesium chloride as the salt of Kovesdi because of the known and disclosed use to preserve viruses. Moreover, at the time of the claimed invention, one or ordinary skill in the art would have been motivated to include MgCl2 in the composition Kovesdi with a reasonable expectation for successfully obtaining a composition for preserving and maintaining viral compositions.

Applicant argues that Kovesdi does not teach trehalose with MgCl2 and that Frei does not teach trehalose.

However, this argument fails to persuade because Kovesdi teaches the compositions wherein trehalose may be combine with MgCl2 (examples). At the time of the claimed invention, one of ordinary skill in the art would have been motivated by Kovesdi to combine any of the disclosed sugar/salt combinations and optimize the volumes of active ingredients as a matter of routine experimentation. Further, one of ordinary skill in the art would have been motivated by the cited references to use MgCl2 and trehalose in combination since they were both well known for preserving viral compositions. Absence of evidence to the contrary, the claimed combination does not appear to impart unexpected benefits or results to the composition obtained by the combined teachings of Kovesdi and Frei, and is therefore rendered obvious.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1 –1 4 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12 – 24 of U.S. Patent No. 6514943 or claims 13 – 20 of U.S. Patent No. 6225289, in view of Evans (US) or Evans (WO).

US Patent 6514943 claims a composition comprising an adenovirus, liquid carrier, and stabilizing agents selected from polysorbate 80, L-arginine, trehalose, or combinations thereof. The composition has 2 – 10% trehalose.

US 6225289 claims a liquid composition comprising adenoviral vector, liquid carrier, and a stabilizing agent selected from polysorbate 80, L-arginine, trehalose and combinations thereof. Specifically, 2 – 10% trehalose, 0.001 – 0.1% polysorbate 80, a buffer and salt.

Although the claims do not teach the composition comprising MgCl2, Evans (US) and Evans (W) teach viral compositions comprising a liquid adenovirus, buffer, sugar, salt, divalent cation and non-ionic detergent. The compositions are disclosed to maintain viral stability for up to 2 years at temperatures of 2 – 8C and higher. Specifically, the composition comprises an adenovirus in an amount of 1x10^7 virus particles/milliliter – 1x10^13 particles/milliliter. Non-ionic surfactants include polysorbate 80 at about 0.001 – 1%, divalent cations include MgCl2 at about 0.1 – 5 mM, and the 2 – 8% sugar/cryoprotectant may be trehalose. Evans teaches the salts are added to attain the desired ionic strength and osmolarity with preferred osmolarties between 200 – 800 mOs/L and a preferred pH of 7.5 – 8.5. Evans teaches that the MgCl2 is necessary for optimum adenovirus stability (example 5).

At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use magnesium chloride as the salt of Kovesdi because of the known and disclosed

use to stabilize, maintain and preserve viruses. Moreover, at the time of the claimed invention, one or ordinary skill in the art would have been motivated to include MgCl2 in the composition Kovesdi with a reasonable expectation for successfully obtaining a composition for preserving and maintaining viral compositions.

In addition, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize the amounts of known effective ingredients as well as the parameters (ionic strength, osmolalities) of the compositions of Kovesdi as a matter of routine experimentation.

Applicant argues that '943 and '289 do not teach trehalose with a divalent salt.

However, these arguments fail to persuade because as indicated above, the Evans' references clearly teach MgCl2 was known to stabilize/preserve viruses. As such, one of ordinary skill in the art would have been motivated to combine MgCl2 with the composition of '943 or '289 with a reasonable expectation for successfully obtaining a composition for preserving viral compositions. Further, absence of evidence to the contrary, the claimed combination does not appear to impart unexpected benefits or results to the composition obtained by the combined teachings of '943/'289 and Evans (US) or (WO).

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-0196. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ruth A. Davis; rad
July 15, 2003

LEON B. LANKFORD, JR.
PRIMARY EXAMINER